BIFUNCTIONAL ENERGY-REVERSIBLE ACYL-COMPOSITIONS

Cross-Reference to Related Applications

This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/284,308, filed April 17, 2001, the contents of which are incorporated herein by reference.

Background of the Invention

The present application relates generally to energy reversible acyl-enzymes. In particular, the present application relates to energy reversible acyl-enzymes and the like having a cinnamate or related structure core and an additional reactive group which can be modified to impart new properties to the whole composition.

Various methods to make use of enzyme inactivation have been disclosed. Enzyme inhibition can be used to enhance long term storage of enzymes or to inactivate the enzymes in a pharmaceutical drug. For example, U.S. Patent No. 5,770,699 describes a process of enzyme inhibition to produce inactivated blood factors. U.S. Patent No. 5,837,679 discloses a method to extend the half lives of blood factors via a transient modification of blood factors by acylation. U.S. Patent No. 4,337,244 reports a method of treating venous thrombosis using an inactivated fibrinolytic enzyme.

Enzyme activity can be controlled with inhibitors. Reversible control of enzyme activity with light has been the focus of a number of reports (see U.S. Patent Nos. 5,114,851 and 5,218,137 to Porter et al.). There are a number of advantages of this concept. Most striking is the ability to control enzyme activity specifically and rapidly, by exposure to light *in vivo* or *ex vivo*.

Porter et al. disclose in U.S. Patent Nos. 5,114,851 and 5,218,137, the light controllable enzymes are obtained by coupling an enzyme active site amino acid residue to cinnamate (CINN) derivatives to form *o*-hydroxy cinnamate substituted esters or acyl enzymes, which are inactive. On photolysis, the bond with the active site amino acid residue is cleaved and the active site is exposed. Pizzo et al. [(1986) Ann. N.Y. Acad. Sci. 485: 199-203] reported on the use of an *o*-hydroxy cinnamate substituted ester, formed by coupling the active site of an enzyme to α-methyl-2-hydroxy-4-diethylaminocinnamic acid.

A subsequent report by Porter, et al. demonstrated the therapeutic potential of the inhibited enzymes. Control of clotting reaction times was concentration dependent and photolysis time dependent. *In vivo* clotting of abnormal blood vessels in a rabbit model of corneal neovascularization was achieved by injection of the inhibited, "caged" enzymes